Lao, Raymond

SCIENCE DIRECT

Lynn Larson is logged in

Home | Publications | Search | My Alerts | My Profile | Help

Brought to you by: the Philip Morris U.S.A. Library

Quick Search: within This Issue Go Search tips

17 of 27 results list | previous | next

The Lancet Oncology
Volume 3, Issue 8, 1 August 2002, Pages 461-469

DOI: 10.1016/S1470-2045(02)00815-X
PII: S1470-2045(02)00815-X
Copyright © 2002 Elsevier Science Ltd. All rights reserved.

This Document
· SummaryPlus
· Full Text + Links
· PDF (1063 K)

Actions
· Cited By
· Save as Citation Alert
· Export Citation

**Reviews**

# Cigarette smoking and lung cancer: chemical mechanisms and approaches to prevention

**Stephen S Hecht**

SSH is Wallin Professor of Cancer Prevention at the University of Minnesota Cancer Center, Minneapolis, MN, USA

Available online 29 July 2002.

## Abstract

Much is now known about the carcinogens in cigarette smoke, their conversion to forms that react with DNA, and the miscoding properties of the resulting DNA adducts that cause the many genetic changes known to exist in human lung cancer. The chronic exposure of pulmonary DNA to a multitude of metabolically activated carcinogens is consistent with our current understanding of cancer as a disease resulting from many changes in key genes regulating growth. This review illustrates how this solid foundation of knowledge can be used to find new ways to prevent lung cancer. Three prevention-related topics are discussed: human uptake of tobacco carcinogens as a way of assessing risk and investigating mechanisms; individual differences in the metabolic activation and detoxification of carcinogens, which may relate to cancer susceptibility; and chemoprevention of lung cancer in smokers and ex-smokers. These new approaches are necessary as adjuncts to education and cessation efforts, which despite some success have not eliminated tobacco smoking.

## Article Outline

• Cigarette-smoke carcinogens
• Human tobacco-carcinogen uptake



PM3006508957

Source: https://www.industrydocuments.ucsf.edu/docs/lghj0001

- Who is susceptible?
- Chemoprevention of lung cancer
- Summary and conclusions
- Search strategy and selection criteria
- Acknowledgements
- References


---

Lung cancer is the most common cancer in the world.[1] It is the leading cause of cancer death in the USA, with over 150000 deaths expected in 2002, [2] and in the UK, where it killed about 34000 people in 2000. [3] About 87% of lung-cancer cases are caused by cigarette smoking ( figure 1).[4]

---

(69K)

Figure 1. Structures of benzo[a]pyrene (top) and nicotine-derived nitrosoamineketone (bottom), two important carcinogens in cigarette smoke.

---

Cigarette smoking causes 30% of all cancer death in the more developed countries.[5] In addition to lung cancer, tobacco smoking is an important cause of oral, oropharyngeal, hypopharyngeal, laryngeal, and oesophageal cancers as well as those of the pancreas, bladder, and renal pelvis. [6] Smoking is also associated with cancers of the nose, stomach, liver, colon, renal body, and cervix, and with myeloid leukaemia. [7 and 8]

Prevention is the most effective way to reduce lung-cancer mortality. The most important step is preventing people from starting to smoke. If they do start, application of viable methods of cessation is essential. These combined methods had substantial impact in the second half of the 20th century. In the USA, the prevalence of smoking among adults decreased from 42• 4% in 1965 to 25• 5% in 1990.[9] There has been a corresponding decrease in the male rate of death from lung cancer. [9] However, smoking prevalence rates in the USA have not changed greatly since 1990. In 1998, overall smoking prevalence among adults was 24• 1%, which corresponds to 47• 2 million people. [10] There were over 1• 1 billion smokers worldwide, consuming about six trillion cigarettes annually. [5] Cigarette smoking is not going to disappear in the near future.

Our goal is to develop new approaches to lung-cancer prevention based on an understanding of tobacco carcinogens. Three lines of research being pursued in our laboratory are discussed here. The first aims to elucidate more clearly how carcinogens are taken up in human beings. Understanding of this process will improve the science base for assessment of human cancer mechanisms and risk. Second, we are studying human carcinogen metabolism to identify individuals who may be highly susceptible to the effects of tobacco carcinogens. And third, we are investigating chemoprevention of lung cancer in current smokers and ex-smokers.



PM3006508958

Source: https://www.industrydocuments.ucsf.edu/docs/lghj0001

# Cigarette-smoke carcinogens

A carcinogen is any agent—chemical, physical, or viral—that causes cancer or increases the incidence of cancer. Among the 4000 identified chemicals in cigarette smoke, more than 60 are established carcinogens, according to assessments by the International Agency for Research on Cancer.[11] These chemical carcinogens are the cause of cancer from cigarette smoke. The strongest carcinogens are polycyclic aromatic hydrocarbons (PAHs), *N*-nitrosamines, and aromatic amines. These compounds occur in small quantities, typically about 5–200 ng per cigarette. The most prevalent carcinogens are aldehydes and other volatile organic compounds such as benzene and butadiene. These compounds are found in quantities of 10–1000 μg per cigarette. In relation to human lung cancer, arguably the most important carcinogens are PAHs such as benzo[*a*]pyrene and the tobacco-specific nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (also known as nicotine-derived nitrosaminoketone [NNK]; figure 1). [12]

Carcinogens form the link between nicotine addiction and lung cancer (figure 2).[12] Nicotine is the reason people continue to smoke despite the well-known adverse effects on health. Nicotine is not generally considered to be a carcinogen, although it can induce tumours under certain special conditions such as hyperoxia. [13] Nicotine can also be converted into carcinogens such as NNK in the body. [14] The cigarette is a disastrous nicotine-delivery device, because more than 60 carcinogens, including PAHs and NNK, accompany nicotine in each puff. Although the dose of each carcinogen per cigarette is quite small, the cumulative dose in a lifetime of smoking is substantial.

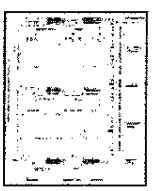
(65K)

Figure 2. Scheme linking cigarette-smoke carcinogens with multiple genetic changes in lung tissue and the development of lung cancer. A key feature is the long-term exposure of DNA to metabolically activated carcinogens resulting in the formation of DNA adducts and resultant genetic changes. This barrage of DNA damage, taking place daily over many years, is fully consistent with multiple genetic changes in lung cancer. The time frame and sequence of genetic changes are uncertain.

The response of the organism to carcinogen exposure is similar to that for any other foreign compound or drug. Cytochrome P450 enzymes catalyse addition of an oxygen atom to the carcinogen, increasing its water solubility and converting it to a form that is more readily excretable. This metabolic detoxification process is further assisted by phase 2 enzymes, which convert the oxygenated carcinogen to a form that is highly soluble in water. To the extent that this process is efficient, the organism will be protected. However, some of the intermediates formed by the interaction of cytochrome P450 enzymes with carcinogens are reactive, generally having an electrophilic (electron-deficient) centre. Such intermediates or metabolites can react with DNA, resulting in the formation of covalently bound products known as DNA adducts. This process, which converts an unreactive carcinogen to a form that binds to DNA, is known as metabolic activation.



PM3006508959

Source: https://www.industrydocuments.ucsf.edu/docs/lghj0001

The balance between metabolic activation and detoxification varies among individuals and is likely to affect cancer risk, because DNA adducts are central to the carcinogenic process.[12 and 15]

Cells have systems for DNA repair that can remove adducts and return the DNA to its normal structure.[16, 17, 18 and 19] There are differences between individuals in DNA repair that can affect cancer risk. [20] Moreover, the repair systems are not completely efficient. Some adducts will escape repair and persist in DNA. These persistent DNA adducts can cause miscoding. For example, when the O6-position of deoxyguanosine in DNA is methylated after metabolic activation of NNK, the resulting DNA adduct (O6-methylguanine) is misread by DNA polymerases as deoxyadenosine, and thymidine is inserted during replication. The consequence is permanent conversion of a G-C base pair to an A-T base pair. This mutation and others can activate oncogenes such as *RAS* or inactivate tumour-suppressor genes such as *p53*. There is much evidence that changes in *RAS* and *p53* result directly from reaction of these genes with metabolically activated carcinogens.[12] Many genetic abnormalities occur during the lung-cancer induction process, including loss of heterozygosity, microsatellite alterations, mutations in *RAS* oncogenes, *MYC* amplification, *BCL2* expression, mutations in the *p53*, *RB*, *p16*, and *FHIT* tumour-suppressor genes, expression of telomerase activity, and others (figure 2). [21 and 22] Although the temporal sequence of mutations is somewhat unclear, we do know that carcinogens can, through the process just described, cause irreversible damage to critical cellular growth-control genes. In smokers, there is a chronic barrage of metabolically activated carcinogens, which cause these multiple changes ( figure 2). This constant assault on genes is completely consistent with genetic derangements leading to six proposed hallmarks of cancer: self-sufficiency in growth signals, insensitivity to antigrowth signals, evasion of apoptosis, tissue invasion and metastasis, sustained angiogenesis, and limitless replicative potential. [23]

# Human tobacco-carcinogen uptake

Our goal is to understand more fully human tobacco-carcinogen uptake. We want to improve our basic comprehension of carcinogen dose and mechanisms of carcinogenesis in humans. We also wish to provide a biochemical foundation for exploring the relation between exposure to environmental tobacco smoke and lung cancer. Environmental tobacco smoke is the term used to describe the material in indoor air that results from tobacco smoking.

Our research in this area has focused on NNK (figure 1 and figure 3).[24] This substance is present in both unburned tobacco (1-2 μg/g) and in cigarette smoke (100-200 ng per cigarette), as confirmed in many international studies. [25] It is not found in materials other than those related to tobacco. NNK is a powerful pulmonary carcinogen, inducing lung tumours in rats, mice, and hamsters whatever the route of administration. [24] F344 rats are particularly susceptible to the carcinogenic effects of NNK. The lowest total dose that can induce lung tumours in rats (1• 8 mg/kg as part of a dose trend) is similar to the total dose of NNK experienced by a smoker in a lifetime of smoking (about 1• 1 mg/kg). [24] DNA-adduct patterns in the lungs of rats and human beings exposed to NNK are also similar. [24] The rodent carcinogenicity data are particularly striking. Lung tumours have been induced, for example, in mice treated with NNK by application to the skin or in rats in which the carcinogen was swabbed in the oral cavity or injected into the urinary bladder. [24] Clearly, NNK is a systemic lung carcinogen, which reaches the lung via the circulation. It induces mainly adenoma and adenocarcinoma of the lung. Two recent epidemiological studies of cigar smokers showed remarkably increased risks of lung cancer compared with non-smokers among cigar smokers who did not inhale, supporting the role of a systemic lung carcinogen as a cause of lung cancer in human beings. [26 and 27] NNK is present in cigar smoke and is the most prevalent systemic lung



PM3006508960

Source: https://www.industrydocuments.ucsf.edu/docs/lghj0001

carcinogen in tobacco smoke. [28] The emergence of adenocarcinoma as the most common type of lung cancer in human beings has also been attributed to NNK, which specifically causes this type of tumour in animals. Amounts of NNK in cigarette smoke have increased during the past two decades in parallel with an increase in adenocarcinoma of the lung, whereas amounts of benzo[*a*]pyrene, a cause of squamous-cell carcinoma of the lung in rodents, have decreased.[11 and 29] Collectively, these observations support the role of NNK as a significant cause of lung cancer in smokers. [24 and 29]

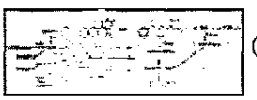
(20K)

Figure 3. Metabolic pathways of benzo[a]pyrene and NNK, modified from references 24 and 46. EH, epoxide hydrolase; BaP, benzo[a]pyrene; GST, glutathione S-transferase; NNAL, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; UGT, UDP-glucuronosyl transferase; P450, cytochrome P450.

When a rodent or human is exposed to NNK, one of the major metabolic events is conversion of the carbonyl group in NNK to an alcohol with the formation of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol(NNAL; figure 3). [24] This product is also a potent pulmonary carcinogen. NNAL in turn is metabolised by glucuronidation of the alcohol and pyridine ring (NNAL glucuronide, figure 3). NNAL and its glucuronides are excreted in the urine. Other pathways of NNK metabolism are illustrated in figure 3. Both NNK and NNAL are metabolically activated by hydroxylation next to the *N*-nitroso group (α-hydroxy-NNK and α-hydroxy-NNAL), leading to formation of DNA adducts. Hydroxylation of the methyl carbon produces pyridyloxobutyl-DNA adducts, and hydroxylation of the methylene carbon produces methyl-DNA adducts. Much evidence implicates both of these pathways in tumour induction by NNK.[24] Other pathways of NNK metabolism include pyridine-*N*-oxide formation and denitrosation, both resulting in NNK detoxification. We have developed an assay for NNAL and its glucuronide in human urine and have used it to study NNK uptake.[30]

We have consistently observed a correlation between concentrations of these substances and of the nicotine metabolites cotinine and cotinine glucuronide in urine (figure 4). Cotinine, a metabolite of nicotine, is commonly used as an uptake biomarker for human exposure to tobacco and other nicotine-containing products. However, nicotine and cotinine are not carcinogenic. Therefore, this measurement does not provide direct information about carcinogen uptake. The correlations shown in figure 4 shows that NNAL and NNAL glucuronide are uptake markers for NNK, thereby providing specific information about human lung-carcinogen uptake.

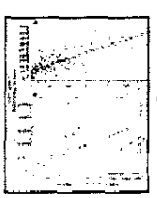
(21K)

Figure 4. Correlation between (a) urinary concentrations of NNAL plus its glucuronide (carcinogen uptake markers) and cotinine plus cotinine glucuronide (nicotine uptake markers) in smokers (r=0• 68, p<0• 01), and (b) children exposed to environmental tobacco smoke (r=0• 71, p<0• 01).[38] Reproduced with



PM3006508961

Source: https://www.industrydocuments.ucsf.edu/docs/lghj0001

permission from Oxford University Press (Carcinogenesis 2002; **23**: 907-22).

---

We have suggested that the ratio of NNAL glucuronide to NNAL may be a biomarker of risk.[30] Since NNAL glucuronide is not carcinogenic but NNAL is, a higher ratio would suggest decreased risk. We have observed that most individuals have ratios ranging from 0• 5 to 5• 0, whereas a small percentage have much higher values ( figure 5). Presumably, smokers with higher ratios would be protected to some extent against the carcinogenic effects of NNK. This finding requires further investigation.

---

(14K)

Figure 5. Ratios of NNAL glucuronide to NNAL in smokers. People with higher ratios may detoxify NNK more effectively and thereby be at lower risk of lung cancer.

---

In one recent study, we quantified urinary NNAL and NNAL glucuronide in people who had stopped smoking.[31] The results showed that these two NNK metabolites are remarkably persistent in the body. A week after smoking cessation, the amount of NNAL plus its glucuronide detected in urine was 34• 5% of the baseline amount, whereas the corresponding proportion for cotinine was 1• 1%. These findings suggest the presence of a high-affinity compartment where NNK or NNAL is sequestered. Further studies showed that one enantiomer of NNAL was stereoselectively retained, which suggests the presence of a receptor site in the lung (eg, $\beta$-adrenergic receptors or nicotinic acetylcholine receptors). [32 and 33] This feature could be related to the high selectivity of NNK for induction of lung tumours.

Environmental tobacco smoke (also known as second-hand smoke) is now widely accepted to be a cause of lung cancer, but the risk is far lower than that in smokers.[34] The NNAL assay is ideally suited to studies of environmental tobacco smoke and cancer, because it has the analytical sensitivity required to detect the low concentrations generally found in urine samples of people exposed to environmental tobacco smoke. More importantly, it is absolutely specific, because NNK is found only in tobacco products. Thus, detection of NNAL and its glucuronide in the urine can be linked only to tobacco exposure, because NNK is not present in the general environment, the diet, or elsewhere.

Our goal has been to investigate the uptake of NNK in non-smokers exposed to environmental tobacco smoke. Our first study was carried out in a chamber under high exposure conditions.[35] We found that concentrations of NNAL plus its glucuronide in urine increased significantly on exposure to these high concentrations of environmental tobacco smoke. In our next study, we showed that workers in a long-term care hospital, who were exposed to environmental tobacco smoke from patients who smoked, had high amounts of NNAL glucuronide in their urine. [36] We then investigated uptake of NNK in women who lived with men who smoked, because most epidemiological studies of environmental tobacco smoke and lung cancer have investigated women



PM3006508962

Source: https://www.industrydocuments.ucsf.edu/docs/lghj0001

with smoking spouses. The uptake of NNK was more than six times higher in women who lived with smokers than in women who lived with non-smokers. [37] In another investigation, widespread uptake of NNK was shown in a group of economically disadvantaged school children. [38] As in smokers, a correlation between concentrations of cotinine and NNAL plus its glucuronide in urine has been consistently observed in non-smokers exposed to environmental tobacco smoke ( figure 4b). The uptake of NNK by non-smokers exposed to environmental tobacco smoke provides a biochemical link between such exposure and lung cancer and strongly supports the concept that environmental tobacco smoke causes lung cancer in humans.

# Who is susceptible?

Less than 20% of smokers get lung cancer.[6] At present, we cannot predict which smoker is susceptible. If we could identify those individuals who would contract cancer on exposure to cigarette smoke, the information could certainly be incorporated into effective prevention strategies.

Figure 2 shows that many factors could influence individual susceptibility to lung cancer in smokers. Among these are extents of carcinogen uptake, metabolic activation, and detoxification; DNA repair ability; apoptosis; and varying effects on genes involved in signal transduction pathways and regulation of the cell cycle. [12 and 39] Our focus is on differences in carcinogen metabolic activation and detoxification. One example of such differences is in ratios of NNAL glucuronide to NNAL. Our present focus in this research is PAH metabolism. Benzo[*a*]pyrene is a prototype PAH. First synthesised in 1933 as part of a programme to identify carcinogens in coal tar, benzo[*a*]pyrene is probably the most extensively studied of all carcinogens.[40] Its ability to induce tumours at the site of application in rodents has been conclusively demonstrated. [41] Benzo[*a*]pyrene and other PAH are thought to be the cause of the carcinogenic effects of occupational exposures to coal tars, soots, and related materials.[42 and 43] Much evidence implicates benzo[*a*]pyrene and other PAH as important carcinogens in tobacco-induced lung cancer in human beings.[12] This evidence includes studies that link the inducibility of benzo[*a*]pyrene-metabolising enzymes to increased pulmonary DNA adducts in vivo and investigations showing that the profile of mutations induced by an ultimate carcinogen of benzo[*a*]pyrene in cells is similar to that seen in the *P53* gene isolated from human lung tumours.[44 and 45]

An overview of benzo[*a*]pyrene metabolism is given in figure 3. [46] In the initial step, various cytochrome P450s catalyse the formation of epoxides and phenols. The epoxides may themselves rearrange spontaneously to phenols (NIH shift) or undergo hydration catalysed by epoxide hydrolase, leading to diols. One of the diols, benzo[*a*]pyrene-7,8-diol, is further oxidised to 7,8-diol-9,10-epoxides in a reaction catalysed by cytochrome P450s as well as other enzymes. One enantiomer of the *anti*-7,8-diol-9,10-epoxide is generally formed to the greatest extent and has the highest carcinogenic activity. This diol epoxide reacts with DNA in vitro and in vivo producing a major adduct, in which the 10 position of the 7,8-diol-9,10-epoxide is bound to the exocyclic amino group of deoxyguanosine in DNA. Convincing evidence clearly supports the hypothesis that the formation of this adduct is the major metabolic activation pathway of benzo[*a*]pyrene. Other pathways of metabolism lead predominantly to detoxification. These include phenol formation, glutathione conjugation of epoxides and diol epoxides involving *GSTM1*, *GSTA1*, and *GSTP1*, and glucuronidation of diols. The roles of catechols produced by dihydrodiol dehydrogenase as well as those of quinones and one-electron oxidation products in the biological activity of benzo[a]pyrene are less clear.

Extensive studies with human tissues clearly show the existence of the benzo[*a*]pyrene metabolism



PM3006508963

Source: https://www.industrydocuments.ucsf.edu/docs/lghj0001

pathways illustrated in figure 3. [41, 44 and 46] These studies have shown large variation between individuals in metabolism and DNA-adduct formation by benzo[*a*]pyrene. These results indicate that humans differ with respect to benzo[*a*]pyrene activation and detoxification. Individuals who activate this compound extensively are thought to be at greater risk of its carcinogenic effects than those who effectively detoxify it. A rapidly growing body of investigations is exploring the relation between polymorphisms, or variants, in benzo[a]pyrene-metabolising genes such as *CYP1A1* and *GSTM1* and cancers of various types.[12, 47 and 48] Variants in *CYP1A1* have been associated with increased lung-cancer risk in Japanese populations, but not in caucasian or African-American populations. The *GSTM1* null genotype, which occurs in 40–50% of people, has been associated with modest increases in lung-cancer risk in smokers. Other studies indicate increased risk of lung cancer in individuals with unfavourable combinations of *CYP1A1* and *GSTM1* genotypes. From the complexity of benzo [*a*]pyrene metabolism as outlined in figure 3, a polymorphism in a single gene is unlikely to be predictive of the outcome of benzo[a]pyrene activation and detoxification. Rational interpretation of genotyping data with respect to carcinogen metabolism will require a more comprehensive approach involving integration of genotyping and phenotyping information. Therefore, we propose to develop an activation/detoxification metabolite profile for benzo[*a*]pyrene or related PAHs. We hope to relate the results of such carcinogen-metabolite phenotyping to genotyping data and find out how variants in benzo[*a*]pyrene-metabolising genes actually relate to metabolite formation and ultimately to cancer.

Our initial work in this area focused on *anti*-benzo[*a*]pyrene-7,8,9,10-tetraol, the product of reaction of *anti*-7,8-diol-9,10-epoxide with water.[49] This metabolite was quantified in urine. The highest concentrations were found in the urine of patients with psoriasis who had been treated with an ointment that contains benzo[*a*]pyrene and other PAH, the next highest in the urine of coke-oven workers, and the lowest in smokers. The low amount in smokers' urine is a reflection of the lower amounts of benzo[*a*]pyrene in present-day cigarettes—only about 10 ng per cigarette. Amounts of *anti*-benzo[*a*]pyrene-7,8,9,10-tetraol in the urine of coke-oven workers correlated with those of 1-hydroxypyrene, a widely used biomarker of PAH uptake.[50] We are continuing our research in this area with the aim of developing a practical phenotyping formula that can be related to risk.

# Chemoprevention of lung cancer

Cancer chemoprevention is the prevention, delay, or reversal of cancer by exposure to agents that alter the process of carcinogenesis. It is a strategy that can be applied in populations at high risk of cancer.[51] Smokers and ex-smokers are clear examples of such high-risk groups. Chemoprevention could logically be coupled with smoking cessation. Smokers who fail in smoking-cessation programmes, as most do, would be candidates for chemoprevention, as would those who successfully stop, because the risk of lung cancer remains high for many years after cessation. [52]

Chemoprevention of lung cancer can be envisioned by considering the steps in figure 2. Retardation or blockage of the steps leading to genetic damage, or stimulation of protective processes, would delay or stop the appearance of lung cancer. There are at present no known chemopreventive agents that are effective against lung cancer in humans. Agents that have failed in clinical trials to date include *N*-acetylcysteine, 13-*cis*-retinoic acid, retinyl palmitate, and β-carotene.[53, 54, 55, 56 and 57] Our goal is to identify and develop effective chemopreventive agents against lung cancer by focusing on the major tobacco-smoke carcinogens NNK and benzo[*a*]pyrene.

Epidemiological studies consistently show that vegetable consumption decreases risk of lung cancer. [1] Therefore, we hypothesise that there are chemopreventive agents in vegetables. In our studies to



PM3006508964

Source: https://www.industrydocuments.ucsf.edu/docs/lghj0001

date, we have focused on isothiocyanates and *myo*-inositol. Cruciferous vegetables such as broccoli, cauliflower, cabbage, mustard, and watercress are rich sources of isothiocyanates, which occur as conjugates called glucosinolates.[58] *Myo*-inositol occurs widely in beans, grains, and nuts.[59] Our interest in isothiocyanates originated in early studies which showed that these compounds inhibited the metabolic activation of NNK. Extensive investigations have now shown that isothiocyanates, as well as *myo*-inositol, are effective inhibitors of tumour development in carcinogen-treated rodents.[60 and 61] The structures of two of our lead isothiocyanate compounds--phenethyl isothiocyanate and benzyl isothiocyanate--as well as *myo*-inositol, are shown in figure 6.

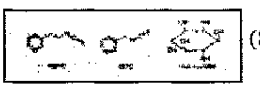
(8K)

Figure 6. Structures of the lung-cancer chemopreventive agents phenethyl isothiocyanate (PEITC), benzyl isothiocyanate (BITC), and myo-inositol.

For the development of effective chemopreventive agents, we envision a grid such as that illustrated in the table for phenethyl isothiocyanate. First, efficacy must be shown in rodent models. Without efficacy, there is no reason to pursue the development of a chemopreventive agent. Second, mechanisms of chemoprevention in rodent models and humans must be understood. To the extent that we can understand mechanisms underlying efficacy in rodents, and show similar mechanisms in humans, we should be able to predict efficacy in humans by a parallelogram approach. Third, chemopreventive agents must have little or no toxicity, because they will be taken regularly by apparently healthy people. Toxicity will negatively affect compliance.

Table 1. Grid for development of phenethyl isothiocyanate as a chemopreventive agent[60, 62, 64 and 66]

(6K)

NNK, nicotine-derived nitrosaminoketone.

Several studies in rats have shown the efficacy of phenethyl isothiocyanate against lung-tumour induction by NNK.[60] In one study, rats were treated with 2 ppm NNK in the drinking water for 2 years. 70% of these rats developed lung tumours. A second group was treated for 2 years with phenethyl isothiocyanate in the diet (498 ppm, a non-toxic dose) and 2 ppm NNK in the drinking water. Only 5% of these rats developed lung tumours; thus, the inhibitory effect was very powerful. Other studies clearly show that phenethyl isothiocyanate is a good inhibitor of NNK-induced lung tumorigenesis in mice. [60] The mechanism by which this agent inhibits tumour induction by NNK in rats is quite well understood. Phenethyl isothiocyanate specifically inhibits cytochrome P450 enzyme (s) in the rat lung, resulting in decreased amounts of pyridyloxobutyl-DNA adducts. [60] Similar effects occur in mice, but other factors such as induction of apoptosis may be involved. [60 and 62] In humans, studies with watercress, a good natural source of phenethyl isothiocyanate, show inhibition of NNK metabolic activation and certain cytochrome P450 enzyme activities. [60] Therefore, there is some parallel between rodent and human mechanistic studies. Phenethyl isothiocyanate is non-toxic in rodents at doses used for chemoprevention and showed no toxic effects in human beings in total



PM3006508965

Source: https://www.industrydocuments.ucsf.edu/docs/lghj0001

doses as high as 160 mg/day, administered orally for 4 weeks.

Although phenethyl isothiocyanate is a strong inhibitor of NNK-induced lung tumorigenesis in rodents, it is inactive against lung-tumour induction by benzo[*a*]pyrene.[60] However, benzyl isothiocyanate is a very effective chemopreventive agent against such tumorigenesis in mice. Benzyl isothiocyanate inhibits cytochrome P450 enzymes and induces phase 2 enzymes. [60 and 63] It slightly decreases DNA-adduct formation by benzo[*a*]pyrene in mouse lung.[64] Induction of apoptosis may have a role in the chemopreventive activity of benzyl isothiocyanate against benzo[*a*]pyrene.[65]

We can therefore envision using phenethyl isothiocyanate and benzyl isothiocyanate in combination for chemoprevention of lung cancer in smokers. A mixture of these agents given in the diet inhibits lung-tumour induction in mice treated with NNK and benzo[*a*]pyrene.[66] Consistently with the chemopreventive activity of isothiocyanates in animal models, three recent epidemiological studies have shown that consumption of isothiocyanate-containing vegetables decreases lung-cancer risk. [67, 68 and 69] Interestingly, glutathione *S*-transferase enzymes seem to have a role here, because they are involved in removal of free isothiocyanates from the body. Therefore, people who have the null variant of these enzymes may be protected.

Dietary *myo*-inositol has shown consistent efficacy against lung-tumour induction by benzo[*a*]pyrene, NNK, or a mixture of these substances.[61 and 70] Chemoprevention has been observed in experiments when *myo*-inositol is given at the same time as the carcinogen, or when it is given after carcinogen administration. A combination of *myo*-inositol and dexamethasone effectively inhibited mouse lung tumorigenesis induced by tobacco smoke.[71] *Myo*-inositol may be effective in ex-smokers. A favourable property of *myo*-inositol is its extremely low toxicity. Humans have been treated with as much as 20 g per day.[61] Although, on a molar basis, *myo*-inositol is a less effective chemopreventive agent than isothiocyanates in some systems, it has a wider therapeutic window because of the low toxicity. We envision *myo*-inositol as an important component of a chemopreventive mixture against lung cancer.

There are limitations to the concept of chemoprevention of tobacco-related cancer. Many argue that it would be a disincentive to cessation. This is a difficult issue with many facets. However, linkage of chemoprevention with smoking cessation as discussed above would perhaps be an acceptable strategy. A second potential problem is low compliance. Use of non-toxic agents would be one way to avert this problem, but there is some question as to whether smokers would comply with a chemoprevention regimen. The problem should be less serious in ex-smokers. A third potential pitfall is that the extensive damage from years of exposure to tobacco carcinogens may be too great for any agent to overcome. However, lung cancer is such a huge problem that even partial success could have a positive impact on thousands of lives. Finally, there is the question of cost. The naturally occurring agents discussed here are not chemically complex and are inexpensive. Although lung-cancer chemoprevention trials in humans have not been successful to date, none of the agents used in those trials was very effective against lung-tumour development in animal models.

## Summary and conclusions

It is often written that "cigarette smoking causes lung cancer but the mechanism is still unclear". The tobacco industry has encouraged such statements as part of its strategy to obscure the truth. The evidence discussed here shows that chemical mechanisms of lung-cancer induction are, in fact, very well understood. We know a great deal about carcinogens in cigarette smoke and the mechanisms by



PM3006508966

Source: https://www.industrydocuments.ucsf.edu/docs/lghj0001

which they react with DNA. We understand the centrality of DNA adducts in carcinogenesis. When we say cancer is a genetic disease we are referring, in the case of lung cancer, to the derangement of cellular control genes by tobacco carcinogens via the chronic reactions of their metabolically activated forms with DNA. This review has discussed three preventive approaches resulting from our understanding of chemical mechanisms of lung-cancer induction by cigarette smoke. They are at different stages of development. Human uptake of tobacco carcinogens is the most mature approach, and the results of these studies are significantly affecting our understanding of mechanisms of human carcinogenesis and risks from exposure to environmental tobacco smoke. Our studies on chemoprevention of tobacco-related cancer have revealed some very effective agents in preclinical studies. The more difficult challenge--to demonstrate efficacy in humans--mainly lies ahead. The identification of susceptible smokers by carcinogen-metabolite phenotyping is a new area of research that may, however, have great promise for prevention. This information is needed not only for development of more effective cessation strategies but also for effective tailoring of chemoprevention.

**Conflict of interest**

None declared.

## Search strategy and selection criteria

Papers cited were identified through Medline. Relevant monographs were also cited. The search focused on authoritative, relevant, relatively recent reviews, papers, and monographs. The coverage of published work is intended to be illustrative rather than comprehensive, to limit the number of references. Only papers published in English were cited.

---

## Acknowledgements

Research in the Hecht laboratory is supported by grants CA-46535, CA-81301, CA-85702, CA-92025, ES-11297, and DA-13333 from the US National Institutes of Health and by grant RP-00-138 from the American Cancer Society. I thank my many colleagues and collaborators who have contributed to our research.

---

## References

1. World Cancer Research Fund, American Institute for Cancer Research. Food, nutrition and the prevention of cancer: a global perspective. Washington, DC: American Institute for Cancer Research, 1997: 37-145.

2. A. Jemal, A. Thomas, T. Murray and M. Thun , Cancer statistics, 2002. *CA Cancer J Clin* **52** (2002), pp. 23-47. Abstract-EMBASE | Abstract-MEDLINE

3. Cancer Research UK. CancerStats: mortality--UK.
http://www.cancerresearchuk.org/images/11632/cancerstats_mortality_2002.pdf (accessed July



PM3006508967

Source: https://www.industrydocuments.ucsf.edu/docs/lghj0001

2002).

4. American Cancer Society. Tobacco use. In: American Cancer Society, (Ed). *Cancer facts & figures 2001*. Atlanta, GA: American Cancer Society, 2001: 29-32.

5. WHOIn: *Tobacco or health: a global status report*, WHO, Geneva (1997), pp. 10-48.

6. International Agency for Research on Cancer, Tobacco smoking. In: *IARCmonographs on the evaluation of the carcinogenic risk of chemicals to humans* **38**, IARC, Lyon (1986), pp. 127-135.

7. R. Doll , Cancers weakly related to smoking. *BMJ* **52** (1996), pp. 35-49. Abstract-EMBASE | Abstract-MEDLINE

8. A. Chao, M.J. Thun, E.J. Jacobs *et al.*, Cigarette smoking and colorectal cancer mortality in the cancer prevention study II. *J Natl Cancer Inst* **92** (2000), pp. 1888-1896. Abstract-MEDLINE | Abstract-EMBASE | Abstract-Elsevier BIOBASE | **Full Text** via CrossRef

9. American Cancer Society. Tobacco use. In: American Cancer Society, (Ed). *Cancer facts & figures 2001*. Atlanta, GA: American Cancer Society, 2001: 4-5.

10. D.S. sds , US Department of Health and Human Services. Cigarette smoking among adults, United States, 1998. *MMWR Morb Mortal Wkly Rep* **48** (2000), pp. 881-884.

11. D. Hoffmann, I. Hoffmann and K. El Bayoumy , The less harmful cigarette: a controversial issue. A tribute to Ernst L Wynder. *Chem Res Toxicol* **14** (2001), pp. 767-790. Abstract-Elsevier BIOBASE | Abstract-EMBASE | Abstract-MEDLINE | **Full Text** via CrossRef

12. S.S. Hecht , Tobacco smoke carcinogens and lung cancer. *J Natl Cancer Inst* **91** (1999), pp. 1194-1210. Abstract-EMBASE | Abstract-MEDLINE | Abstract-Elsevier BIOBASE | **Full Text** via CrossRef

13. H.M. Schuller, M.D. McGavin, M. Orloff *et al.*, Simultaneous exposure to nicotine and hyperoxia causes tumors in hamsters. *Lab Invest* **73** (1995), pp. 448-456. Abstract-MEDLINE | Abstract-Elsevier BIOBASE | Abstract-EMBASE

14. S.S. Hecht, J.B. Hochalter, P.W. Villalta and S.E. Murphy , 2'-hydroxylation of nicotine by cytochrome P450 2A6 and human liver microsomes: formation of a lung carcinogenic precursor. *Proc Natl Acad Sci USA* **97** (2000), pp. 12493-12497. Abstract-MEDLINE | Abstract-EMBASE | Abstract-BIOTECHNOBASE | Abstract-Elsevier BIOBASE | **Full Text** via CrossRef

15. D. Tang, D.H. Phillips, M. Stampfer *et al.*, Association between carcinogen-DNA adducts in white blood cells and lung cancer risk in the physicians health study. *Cancer Res* **61** (2001), pp. 6708-6712. Abstract-Elsevier BIOBASE | Abstract-BIOTECHNOBASE | Abstract-MEDLINE | Abstract-EMBASE



PM3006508968

Source: https://www.industrydocuments.ucsf.edu/docs/lghj0001

16. A. Memisoglu and L. Samson , Base excision repair in yeast and mammals. *Mutat Res* **451** (2000), pp. 39-51. SummaryPlus | Full Text + Links | PDF (204 K)

17. C.J. Norbury and I.D. Hickson , Cellular responses to DNA damage. *Annu Rev Pharmacol Toxicol* **41** (2001), pp. 367-401. Abstract-MEDLINE | Abstract-EMBASE | Abstract-Elsevier BIOBASE | **Full Text** via CrossRef

18. P.C. Hanawalt , Controlling the efficiency of excision repair. *Mutat Res* **485** (2001), pp. 3-13. SummaryPlus | Full Text + Links | PDF (91 K)

19. A.E. Pegg , Repair of O-6-alkylguanine by alkyltransferases. *Mutat Res* **462** (2000), pp. 83-100. SummaryPlus | Full Text + Links | PDF (152 K)

20. Q. Wei, L. Cheng, C.I. Amos *et al.*, Repair of tobacco carcinogen-induced DNA adducts and lung cancer risk: a molecular epidemiologic study. *J Natl Cancer Inst* **92** (2000), pp. 1764-1772. Abstract-MEDLINE | Abstract-EMBASE | Abstract-Elsevier BIOBASE

21. Y. Sekido, K.W. Fong and J.D. Minna , Progress in understanding the molecular pathogenesis of human lung cancer. *Biochim Biophys Acta* **1378** (1998), pp. F21-F59. Abstract | Full Text + Links | PDF (516 K)

22. I.J. Wistuba, S. Lam, C. Behrens *et al.*, Molecular damage in the bronchial epithelium of current and former smokers. *J Natl Cancer Inst* **89** (1997), pp. 1366-1372.

23. D. Hanahan and R.A. Weinberg , The hallmarks of cancer. *Cell* **100** (2000), pp. 57-70. Abstract-EMBASE | Abstract-BIOTECHNOBASE | Abstract-Elsevier BIOBASE | Abstract-MEDLINE

24. S.S. Hecht , Biochemistry, biology, and carcinogenicity of tobacco-specific *N*-nitrosamines. *Chem Res Toxicol* **11** (1998), pp. 559-603. Abstract-MEDLINE | Abstract-Elsevier BIOBASE | Abstract-Beilstein Abstracts | Abstract-EMBASE | **Full Text** via CrossRef

25. B. Spiegelhalder and H. Bartsch , Tobacco-specific nitrosamines. *Eur J Cancer Prev* **5** (1996), pp. 33-38. Abstract-MEDLINE | Abstract-EMBASE

26. P. Boffetta, G. Pershagen, K.H. Jockel *et al.*, Cigar and pipe smoking and lung cancer risk: a multicenter study from Europe. *J Natl Cancer Inst* **91** (1999), pp. 697-701. Abstract-Elsevier BIOBASE | Abstract-EMBASE | Abstract-MEDLINE | **Full Text** via CrossRef

27. J.A. Shapiro, E.J. Jacobs and M.J. Thun , Cigar smoking in men and risk of death from tobacco-related cancers. *J Natl Cancer Inst* **92** (2000), pp. 333-337. Abstract-EMBASE | Abstract-Elsevier BIOBASE | Abstract-MEDLINE | **Full Text** via CrossRef

28. S.S. Hecht and D. Hoffmann , Re: Cigar smoking in men and risk of death from tobacco-related cancers. *J Natl Cancer Inst* **92** (2000), p. 2040. Abstract-EMBASE | Abstract-MEDLINE | Abstract-



PM3006508969

Source: https://www.industrydocuments.ucsf.edu/docs/lghj0001

Elsevier BIOBASE | **Full Text** via CrossRef

29. E.L. Wynder and D. Hoffmann , Smoking and lung cancer: scientific challenges and opportunities. *Cancer Res* **54** (1994), pp. 5284-5295. Abstract-EMBASE | Abstract-BIOTECHNOBASE | Abstract-Elsevier BIOBASE | Abstract-MEDLINE

30. S.G. Carmella, S. Akerkar, J.P. Richie, Jr and S.S. Hecht , Intraindividual and interindividual differences in metabolites of the tobacco-specific lung carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) in smokers' urine. *Cancer Epidemiol Biomarkers Prev* **4** (1995), pp. 635-642. Abstract-MEDLINE | Abstract-EMBASE

31. S.S. Hecht, S.G. Carmella, M. Chen *et al.*, Quantitation of urinary metabolites of a tobacco-specific lung carcinogen after smoking cessation. *Cancer Res* **59** (1999), pp. 590-596. Abstract-MEDLINE | Abstract-EMBASE | Abstract-BIOTECHNOBASE

32. S.S. Hecht, S.G. Carmella, M. Ye *et al.*, Quantitation of metabolites of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone after cessation of smokeless tobacco use. *Cancer Res* **62** (2002), pp. 129-134. Abstract-MEDLINE | Abstract-EMBASE | Abstract-BIOTECHNOBASE | Abstract-Elsevier BIOBASE

33. H.M. Schuller, P.K. Tithof, M. Williams and H. Plummer, III , The tobacco-specific carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone is a $\beta$-adrenergic agonist and stimulates DNA synthesis in lung adenocarcinoma via $\beta$-adrenergic receptor-mediated release of arachidonic acid. *Cancer Res* **59** (1999), pp. 4510-4515. Abstract-BIOTECHNOBASE | Abstract-Elsevier BIOBASE | Abstract-EMBASE | Abstract-MEDLINE

34. National Cancer Institute. Health effects of exposure to environmental tobacco smoke: the report of the California Environmental Protection Agency. *Smoking and tobacco control monograph 10.* Bethesda: US Department of Health and Human Services, National Institutes of Health, National Cancer Institute, 1999: NIH publication number 99-4645.

35. S.S. Hecht, S.G. Carmella, S.E. Murphy *et al.*, A tobacco-specific lung carcinogen in the urine of men exposed to cigarette smoke. *N Engl J Med* **329** (1993), pp. 1543-1546. Abstract-MEDLINE | Abstract-EMBASE | **Full Text** via CrossRef

36. W.D. Parsons, S.G. Carmella, S. Akerkar *et al.*, A metabolite of the tobacco-specific lung carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) in the urine of hospital workers exposed to environmental tobacco smoke. *Cancer Epidemiol Biomarkers Prev* **7** (1998), pp. 257-260. Abstract-MEDLINE | Abstract-Elsevier BIOBASE | Abstract-EMBASE

37. K.E. Anderson, S.G. Carmella, M. Ye *et al.*, Metabolites of a tobacco-specific lung carcinogen in the urine of nonsmoking women exposed to environmental tobacco smoke in their homes. *J Natl Cancer Inst* **93** (2001), pp. 378-381. Abstract-MEDLINE | Abstract-EMBASE | Abstract-Elsevier BIOBASE | **Full Text** via CrossRef

38. S.S. Hecht, M. Ye, S.G. Carmella *et al.*, Metabolites of a tobacco-specific lung carcinogen in the



PM3006508970

Source: https://www.industrydocuments.ucsf.edu/docs/lghj0001

urine of elementary school-aged children. *Cancer Epidemiol Biomarkers Prev* **10** (2001), pp. 1109_1116. Abstract-MEDLINE | Abstract-EMBASE

39. F.P. Perera , Environment and cancer: who are susceptible?. *Science* **278** (1997), pp. 1068_1073. Abstract-EMBASE | Abstract-MEDLINE | **Full Text** via CrossRef

40. D.H. Phillips , Fifty years of benzo[*a*]pyrene. *Nature* **303** (1983), pp. 468_472. Abstract-EMBASE | Abstract-MEDLINE

41. International Agency for Research on Cancer, Polynuclear aromatic compounds: part 1, chemical, environmental, and experimental data. In: *IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans* **32**, IARC, Lyon (1983), pp. 211_224.

42. International Agency for Research on Cancer, Polynuclear aromatic compounds: part 3, industrial exposures in aluminum production, coal gasification, coke production, and iron and steel founding. In: *IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans* **34**, IARC, Lyon (1984), pp. 65_131.

43. International Agency for Research on Cancer, Polynuclear aromatic compounds: part 4, bitumens, coal-tars and derived products, shale-oils and soots. In: *IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans* **35**, IARC, Lyon (1985), pp. 83_247.

44. H. Bartsch , DNA adducts in human carcinogenesis: etiological relevance and structure-activity relationship. *Mutat Res* **340** (1996), pp. 67_79. Abstract-MEDLINE

45. M.F. Denissenko, A. Pao, M. Tang and G.P. Pfeifer , Preferential formation of benzo[*a*]pyrene adducts at lung cancer mutational hot spots in P53. *Science* **274** (1996), pp. 430_432. Abstract-Elsevier BIOBASE | Abstract-MEDLINE | **Full Text** via CrossRef

46. C.S. Cooper, P.L. Grover and P. Sims , The metabolism and activation of benzo[*a*]pyrene. In: J.W. Bridge and L.F. Chasseaud, Editors, *Progress in drug metabolism* (7th edn ed.),, John Wiley & Sons, Chichester (1983), pp. 295_396.

47. H. Bartsch, U. Nair, A. Risch *et al.*, Genetic polymorphism of CYP genes, alone or in combination, as a risk modifier of tobacco-related cancers. *Cancer Epidemiol Biomarkers Prev* **9** (2000), pp. 3_28. Abstract-EMBASE | Abstract-MEDLINE | Abstract-Elsevier BIOBASE

48. G.B. Smith, P.A. Harper, J.M. Wong *et al.*, Human lung microsomal cytochrome P4501A1 (CYP1A1) activities: impact of smoking status and CYP1A1, aryl hydrocarbon receptor, and glutathione S-transferase M1 genetic polymorphisms. *Cancer Epidemiol Biomarkers Prev* **10** (2001), pp. 839_853. Abstract-Elsevier BIOBASE | Abstract-EMBASE | Abstract-MEDLINE

49. C.D. Simpson, M.T. Wu, D.C. Christiani *et al.*, Determination of r-7,t-8,9,c-10-tetrahydroxy-7,8,9,10-tetrahydrobenzo[*a*]pyrene in human urine by gas chromatography-negative ion chemical ionization-mass spectrometry. *Chem Res Toxicol* **13** (2000), pp. 271_280. Abstract-EMBASE |



PM3006508971

Source: https://www.industrydocuments.ucsf.edu/docs/lghj0001

Abstract-Elsevier BIOBASE | Abstract-MEDLINE | **Full Text** via CrossRef

50. M.T. Wu, C.D. Simpson, D.C. Christiani and S.S. Hecht , Relationship of exposure to coke-oven emissions and urinary metabolites of benzo[*a*]pyrene and pyrene in coke-oven workers. *Cancer Epidemiol Biomarkers Prev* **11** (2002), pp. 311-314. Abstract-MEDLINE | Abstract-EMBASE | Abstract-Elsevier BIOBASE

51. B. Fisher, J.P. Costantino, D.L. Wickerham *et al.*, Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 study. *J Natl Cancer Inst* **90** (1998), pp. 1371-1388. Abstract-MEDLINE | Abstract-EMBASE | **Full Text** via CrossRef

52. W.J. Blot and J.F. Fraumeni, Jr , Cancers of the lung and pleura. In: D. Schottenfeld and J. Fraumeni, Editors, *Cancer epidemiology and prevention*, Oxford University Press, New York (1996), pp. 637-665.

53. D. Albanes, O.P. Heinonen, P.R. Taylor *et al.*, Alpha-tocopherol and beta-carotene supplements and lung cancer incidence in the alpha-tocopherol, beta-carotene cancer prevention study: effects of base-line characteristics and study compliance. *J Natl Cancer Inst* **88** (1996), pp. 1560-1570. Abstract-Elsevier BIOBASE | Abstract-MEDLINE | Abstract-EMBASE | **Full Text** via CrossRef

54. C.H. Hennekens, J.E. Buring, J.E. Manson *et al.*, Lack of effect of long-term supplementation with beta carotene on the incidence of malignant neoplasms and cardiovascular disease. *N Engl J Med* **334** (1996), pp. 1189-1190.

55. S.M. Lippman, J.J. Lee, D.D. Karp *et al.*, Randomized phase III intergroup trial of isotretinoin to prevent second primary tumors in stage I non-small-cell lung cancer. *J Natl Cancer Inst* **93** (2001), pp. 605-618. Abstract-MEDLINE | **Full Text** via CrossRef

56. G.S. Omenn, G.E. Goodman, M.D. Thornquist *et al.*, Effects of the combination of beta carotene and vitamin A on lung cancer and cardiovascular disease. *N Engl J Med* **334** (1996), pp. 1150-1155. Abstract-EMBASE | Abstract-MEDLINE | **Full Text** via CrossRef

57. N. van Sanwijk, O. Dalesio, U. Pastorino *et al.*, EUROSCAN, a randomized trial of vitamin A and N-acetylcysteine in patients with head and neck cancer or lung cancer. *J Natl Cancer Inst* **92** (2000), pp. 977-986.

58. J.W. Fahey, A.T. Zalcmann and P. Talalay , The chemical diversity and distribution of glucosinolates and isothiocyanates among plants. *Phytochemistry* **56** (2001), pp. 5-51. Abstract | Full Text + Links | PDF (422 K)

59. R.S. Clements, Jr and B. Darnell , *Myo*-inositol content of common foods: development of a high myo-inositol diet. *Am J Clin Nutr* **33** (1980), pp. 1954-1967. Abstract-MEDLINE

60. S.S. Hecht , Inhibition of carcinogenesis by isothiocyanates. *Drug Metabol Rev* **32** (2000), pp. 395-411. Abstract-MEDLINE | Abstract-Elsevier BIOBASE | Abstract-EMBASE | **Full Text** via



PM3006508972

Source: https://www.industrydocuments.ucsf.edu/docs/lghj0001

CrossRef

61. S.S. Hecht, P.M.J. Kenney, M. Wang and P. Upadhyaya , Dose-response study of *myo*-inositol as an inhibitor of lung tumorigenesis induced in A/J mice by benzo[*a*]pyrene and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butane. *Cancer Lett* **167** (2000), pp. 1-6.

62. Sticha KRK, Kenney PMJ, Boysen G, et al. Effects of benzyl isothiocyanate and phenethyl isothiocyanate on DNA adduct formation by a mixture of benzo[*a*]pyrene and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone in A/J mouse lung. *Carcinogenesis*, in press.

63. Y. Zhang and P. Talalay , Anticarcinogenic activities of organic isothiocyanates: chemistry and mechanism. *Cancer Res* **54** suppl (1994), pp. 1976s-1981s.

64. K.R.K. Sticha, M.E. Staretz, M. Wang *et al.*, Effects of benzyl isothiocyanate and phenethyl isothiocyanate on benzyl[*a*]pyrene metabolism and DNA adduct formation in the A/J mouse. *Carcinogenesis* **21** (2000), pp. 1711-1719. Abstract-Elsevier BIOBASE | Abstract-EMBASE | Abstract-MEDLINE | **Full Text** via CrossRef

65. Y.R. Chen, W. Wang, A.N.T. Kong and T.H. Tan , Molecular mechanisms of c-Jun N-terminal kinase-mediated apoptosis induced by anticarcinogenic isothiocyanates. *J Biol Chem* **273** (1998), pp. 1769-1775. Abstract-EMBASE | Abstract-BIOTECHNOBASE | Abstract-MEDLINE | **Full Text** via CrossRef

66. S.S. Hecht, P.M.J. Kenney, W. Wang *et al.*, Effects of phenethyl isothiocyanate and benzyl isothiocyanate, individually and in combination, on lung tumorigenesis induced in A/J mice by benzo [*a*]pyrene and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone. *Cancer Lett* **150** (1999), pp. 49-56.

67. S.J. London, J.M. Yuan, F.L. Chung *et al.*, Isothiocyanates, glutathione S-transferase M1 and T1 polymorphisms, and lung-cancer risk: a prospective study of men in Shanghai, China. *Lancet* **356** (2000), pp. 724-729. Abstract | Full Text + Links | PDF (98 K)

68. M.R. Spitz, C.M. Duphorne, M.A. Detry *et al.*, Dietary intake of isothiocyanates: evidence of a joint effect with glutathione S-transferase polymorphisms in lung cancer risk. *Cancer Epidemiol Biomarkers Prev* **9** (2000), pp. 1017-1020. Abstract-MEDLINE | Abstract-EMBASE | Abstract-Elsevier BIOBASE

69. B. Zhao, A. Seow, E.J. Lee *et al.*, Dietary isothiocyanates, glutathione S-transferase -M1, -T1 polymorphisms and lung cancer risk among Chinese women in Singapore. *Cancer Epidemiol Biomarkers Prev* **10** (2001), pp. 1063-1067. Abstract-MEDLINE | Abstract-BIOTECHNOBASE | Abstract-EMBASE | Abstract-Elsevier BIOBASE

70. L.W. Wattenberg and R.D. Estensen , Chemopreventive effects of *myo*-inositol and dexamethasone on benzo[*a*]pyrene and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone-induced pulmonary carcinogenesis in female A/J mice. *Cancer Res* **56** (1996), pp. 5132-5135. Abstract-EMBASE | Abstract-BIOTECHNOBASE | Abstract-Elsevier BIOBASE | Abstract-MEDLINE



PM3006508973

Source: https://www.industrydocuments.ucsf.edu/docs/lghj0001

71. H. Witschi, I. Espiritu and D. Uyeminami , Chemoprevention of tobacco smoke-induced lung tumors in A/J strain mice with dietary *myo*-inositol and dexamethasone. *Carcinogenesis* **20** (1999), pp. 1375-1378. Abstract-MEDLINE | Abstract-EMBASE | Abstract-Elsevier BIOBASE | **Full Text** via CrossRef

**Correspondence:** Dr Stephen S Hecht, University of Minnesota Cancer Center, MMC 806, 420 Delaware Street SE, , Minneapolis, MN 55455, , USA. Tel: +1 612 624 7604. Fax: +1 612 626 5135; email: hecht002@umn.edu

**The Lancet Oncology**
Volume 3, Issue 8, 1 August 2002, Pages 461-469



Send feedback to ScienceDirect
*Software and compilation © 2002 ScienceDirect. All rights reserved.*
*ScienceDirect® is an Elsevier Science B.V. registered trademark.*

Your use of this service is governed by Terms and Conditions. Please review our Privacy Policy for details on how we protect information that you supply.



PM3006508974

Source: https://www.industrydocuments.ucsf.edu/docs/lghj0001